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Reaching an ACCORD on Glycemia and Systolic Blood Pressure Targets in Type 2 Diabetes Mellitus

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Patients with type 2 diabetes mellitus experience microvascular and macrovascular complications from their condition. Microvascular complications include renal, retinal, and neuropathic disease. Macrovascular complications include coronary, cerebrovascular, and peripheral arterial diseases that lead to premature cardiovascular death.

These complications are competing risks. Dying at a young age from macrovascular disease means that some subjects with diabetes mellitus do not have the opportunity to develop advanced microvascular disease.

Studies of diabetes mellitus medications that have reduced cardiovascular events have previously used single-agent interventions that have resulted in only modest reductions in glucose control (usually with a glycated hemoglobin still >7.0%), and the beneficial effects may have been medication rather than glucose-control related. Thus, the UKPDS (UK Prospective Diabetes Study) found a reduction in cardiovascular events with metformin in a study of overweight newly diagnosed patients free from symptoms on a diet and followed up for ≈ 11 years, with a reduction in glycated hemoglobin from 8.0% to 7.4%.¹ A trial of liraglutide, a glucagon-like peptide-1 receptor agonist, decreased glycated hemoglobin by 0.4% from 8.7% and systolic blood pressure (SBP) by 1.2 mm Hg and reduced cardiovascular events significantly.² However, another glucagon-like peptide-1 receptor agonist that reduced glycated hemoglobin by between 0.7% and 1% (depending on randomized dose) from a baseline of 8.7%, and also lowered SBP by 1.3 to 2.6 mm Hg, decreased nonfatal but not fatal cardiovascular events while actually increasing retinopathy.³ More recently,

treatment with sodium-glucose cotransporter-2 inhibitors (eg, empagliflozin) had reduced glycated hemoglobin by $\approx 0.5\%$ to 0.6% (depending on the dose used) from a baseline of $\approx 8.1\%$ and mainly reduced cardiovascular death and heart failure (possibly at least in part by lowering SBP by 4 mm Hg).⁴

All of these trials of diabetes mellitus medications decreased glycated hemoglobin modestly and cannot really be used to compare “tight” glycemic control with standard glycemic control.

To date, tight glycemic control versus standard control has not been shown to prevent macrovascular disease but has led to reductions in microvascular complications.⁵ Managing traditional cardiovascular risk factors, such as lowering blood pressure, treating dyslipidemia, and increasing exercise and smoking cessation, unquestionably reduces macrovascular disease and leads to prolonged survival.

The ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) study was a 2×2 factorial design study that tested intensive (<120 mm Hg) versus standard (<140 mm Hg) SBP control and intensive (<6% glycated hemoglobin) versus standard (7.0%–7.9% glycated hemoglobin) glycemic control in subjects with type 2 diabetes mellitus.⁶ The trial results caused some consternation, with intensive glucose control increasing mortality and intensive SBP control having no significant effect.

The article by Beddhu and others in this issue of the *Journal of the American Heart Association (JAHA)* casts light on the blood pressure aspect of the ACCORD BP study.⁷ The authors have investigated why the ACCORD BP study blood pressure results were different from those of the SPRINT (Systolic Blood Pressure Intervention Trial), which showed benefits of the same lower SBP target of 120 mm Hg versus 140 mm Hg in subjects who did not have diabetes mellitus.

SPRINT reported a reduction in the composite primary cardiovascular outcome of time to the first event of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, acute decompensated heart failure, or death from cardiovascular disease causes.⁸ A significant reduction in this composite primary end point was found and was driven to a large part by fewer cardiovascular deaths and fewer

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cases of decompensated heart failure. The ACCORD BP study primary end point was similar to the SPRINT composite end point but excluded acute coronary syndrome and decompensated heart failure. To better compare the 2 trials, Beddhu et al⁷ defined a modified ACCORD BP study end point by adding to the primary outcome congestive heart failure and unstable angina events that occurred (which presumably closely resemble acute decompensated heart failure and acute coronary syndrome reported in SPRINT). They then compared the ACCORD BP study modified primary end points in those subjects randomized to the standard glycemic control and intensive glycemic control arms of the ACCORD BP study.

There were some other differences between the ACCORD BP study and SPRINT. The ACCORD BP study was a much smaller study and the demographics differed, with ACCORD BP study subjects being younger, being more often women, and having a higher body mass index among other things. However, BP lowering was similar.

The most interesting finding of this post hoc analysis was that SBP lowering in the ACCORD BP study decreased the hazard of the composite end point or mortality in the ACCORD BP study similarly to SPRINT in the standard glycemic control arm but not in the intensive glycemic control arm.

The mechanism of why the double intervention of intensive SBP and intensive glycemic control was so different from intensive SBP and standard glycemic control will be the subject of speculation and debate. It seems that lowering SBP to 120 mm Hg in patients with type 2 diabetes mellitus is beneficial in preventing macrovascular disease as long as one does not also strive for intensive glucose control.

The overall message for physicians treating patients with type 2 diabetes mellitus is that tight glucose control should be avoided and instead clinicians should focus their skills at reducing SBP, cholesterol, and smoking while encouraging weight loss and regular exercise, a message that has been wisely stated by others.⁹

It is not a good outcome for patients with diabetes mellitus to die early with good eyesight or reduced proteinuria. Avoiding tight glycemic control allows patients with diabetes mellitus to reap the considerable benefits of an SBP target of ≤ 120 mm Hg.

It is time to change practice.

Disclosures

In the past 2 years, the department of MacDonald and Mackenzie has held research grants from Novartis, Pfizer, Amgen, RTI Health Solutions, George Clinical, Ipsen, and Teijin & Menarini. MacDonald has been the Principal Investigator on trials paid for by Pfizer, Novartis, Ipsen, and Teijin & Menarini. MacDonald has been paid consulting or speakers fees by Novartis. Mackenzie has been the Principal Investigator on trials paid for by Amgen and Menarini and has received educational meeting attendance supported by Amgen.

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